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Unconventional Views of Frailty

Frailty and Risk of Falls, Fracture, and Mortality in Older Women: The Study of Osteoporotic Fractures

Kristine E. Ensrud,[1,2] Susan K. Ewing,[3] Brent C. Taylor,[1] Howard A. Fink,[1,2] Katie L. Stone,[4] Jane A. Cauley,[5] J. Kathleen Tracy,[6] Marc C. Hochberg,[7] Nicolas Rodondi,[8] and Peggy M. Cawthon,[4] for the Study of Osteoporotic Fractures Research Group

[1]Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, Minnesota.
[2]Department of Medicine and Division of Epidemiology and Community Health, University of Minnesota, Minneapolis.
[3]Department of Epidemiology and Biostatistics, University of California, San Francisco.
[4]Research Institute, California Pacific Medical Center, San Francisco.
[5]Department of Epidemiology, University of Pittsburgh, Pennsylvania.
Departments of [6]Epidemiology and [7]Medicine, University of Maryland, Baltimore.
[8]University Outpatient Clinic and Institute of Social and Preventive Medicine, Department of Community Medicine and Public Health, University of Lausanne, Switzerland.

Background. A standard phenotype of frailty was associated with an increased risk of adverse outcomes including mortality in a recent study of older adults. However, the predictive validity of this phenotype for fracture outcomes and across risk subgroups is uncertain.

Methods. To determine whether a standard frailty phenotype was independently associated with risk of adverse health outcomes in older women and to evaluate the consistency of associations across risk subgroups defined by age and body mass index (BMI), we ascertained frailty status in a cohort of 6724 women $\geq$ 69 years and followed them prospectively for incident falls, fractures, and mortality. Frailty was defined by the presence of three or more of the following criteria: unintentional weight loss, weakness, self-reported poor energy, slow walking speed, and low physical activity. Incident recurrent falls were defined as at least two falls during the subsequent year. Incident fractures (confirmed with x-ray reports), including hip fractures, and deaths were ascertained during an average of 9 years of follow-up.

Results. After controlling for multiple confounders such as age, health status, medical conditions, functional status, depressive symptoms, cognitive function, and bone mineral density, frail women were subsequently at increased risk of recurrent falls (multivariate odds ratio = 1.38, 95% confidence interval [CI], 1.02–1.88), hip fracture (multivariate hazards ratio [MHR] = 1.40, 95% CI, 1.03–1.90), any nonspine fracture (MHR = 1.25, 95% CI, 1.05–1.49), and death (MHR = 1.82, 95% CI, 1.56–2.13). The associations between frailty and these outcomes persisted among women $\geq$ 80 years. In addition, associations between frailty and an increased risk of falls, fracture, and mortality were consistently observed across categories of BMI, including BMI $\geq$ 30 kg/m^2.

Conclusion. Frailty is an independent predictor of adverse health outcomes in older women, including very elderly women and older obese women.

FRAILTY is frequently defined variably and has not yet emerged as a discrete clinical syndrome (1,2). In an attempt to standardize the definition of frailty, Fried and colleagues (3), using data from the Cardiovascular Health Study (CHS), proposed a phenotype of frailty in which three or more of the following five components were present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. Findings from their analysis suggested that frail older adults were at an increased risk of subsequent falls, hospitalization, disability, and mortality. Another large study of postmenopausal women aged 65–79 years (4) reported an association between this phenotype and risk of hip fracture, but no prior study has examined the relationship between frailty and other fracture types. In addition, the predictive validity of this phenotype across risk subgroups is uncertain.

Although prior studies including the analysis from the CHS cohort have consistently reported that frailty is increasingly common with advancing age (3–5) and is more frequently observed in women as compared with men (3,5,6), it is unknown whether the association between frailty and adverse health outcomes in older women persists among the oldest old. In addition, whereas frailty is traditionally considered a wasting disorder common in underweight elderly persons (7), a recent study in older women (8) reported that obese women were more likely than nonobese women to be classified in the intermediate (prefrail) and frail categories. Yet it is uncertain whether the association between frailty and subsequent risk for morbidity and mortality is consistently observed among underweight, normal weight, overweight, and obese women.

We used data collected in the Study of Osteoporotic Fractures (SOF) to examine whether the frailty phenotype,

as defined by Fried and colleagues, was independently associated with adverse health outcomes including recurrent falls, fractures, and mortality in a cohort of 6724 community-dwelling women aged 69 years and older, and evaluated whether these associations were consistent across risk subgroups defined by age and body mass index (BMI).

Methods

Participants

From September 1986 to October 1988, a total of 9704 women at least 65 years old were recruited for participation in the baseline examination of the prospective SOF study. Women were recruited from population-based listings in four areas of the United States (9). Black women were originally excluded from SOF because of their low incidence of hip fracture. In addition, women were excluded if they were unable to walk without assistance or had a history of bilateral hip replacement.

All surviving participants were invited to participate in a fourth examination between 1992 and 1994. A total of 8412 women (97% of survivors as of July 31, 1994) completed at least the questionnaire component of this examination. Of these, 6724 women provided data for at least three frailty components among the five frailty criteria and are the subject of this analysis.

Measurements

Participants completed a questionnaire and were interviewed during the fourth examination and asked about health status, education, smoking history, intention to lose weight, and falls during the previous year. A selected medical history was obtained, including a history of physician diagnosis of fracture since the age of 50 years, stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and cancer (except skin cancer). Participants were asked to bring all prescription and nonprescription medications, including estrogen preparations, with them to clinic for verification of use. Physical activity was assessed using a modified version of the Harvard Alumni Questionnaire (10,11) and was expressed as a weighted score of kilocalories expended per week. Depressive symptoms including the question, ''Do you feel full of energy?'' were evaluated using the 15-item Geriatric Depression Scale (12). Cognitive function was assessed with a modified version of the Mini-Mental State Examination (13) with a maximum score of 26. To assess functional disability, women were asked whether they had any difficulty performing any of five independent activities of daily living (IADL) (14). Tests of physical function included grip strength (using a handheld Jamar dynamometer) and walk speed (time in seconds to walk 6 meters at usual pace). Body weight was recorded with a balance beam scale at both examinations. Height was measured using a standard held-expiration technique with a wall-mounted Harpenden stadiometer (Holtain, U.K.). Height and weight were used to calculate a standard BMI. Bone mineral density of the proximal femur was measured using dual energy x-ray absorptiometry (QDR 1000; Hologic, Waltham, MA).

Frailty

Frailty was operationally defined at the fourth examination using criteria proposed by Fried and colleagues (3) using data collected in the CHS study. Frailty was identified by the presence of three or more of the following components:

1. *Shrinking*, as identified by an unintentional weight loss of $\geq$ 5% between the third and fourth examination (mean years between examinations 2.0 $\pm$ 0.3);
2. *Weakness*, as identified at the fourth examination by a grip strength in the lowest quintile stratified by BMI (quartiles);
3. *Poor energy*, as identified at the fourth examination by an answer of ''no'' to the question ''Do you feel full of energy?'' on the Geriatric Depression Scale (12);
4. *Slowness*, as identified at the fourth examination by a walk speed in the lowest quintile stratified by standing height (median); and
5. *Low physical activity* level at the fourth examination, as identified by a weighted score of kilocalories expended per week in the lowest quintile.

Women with none of the above components were considered to be robust, and those with one or two components were considered to be in an intermediate or prefrail stage.

Ascertainment of Falls, Fractures, and Mortality

After the fourth examination, we contacted participants about falls and fractures every 4 months by postcard or telephone and were able to complete 98% of these contacts in surviving women. All falls reported on the first three postcards returned after the fourth examination (covering approximately 1 year) were included in the falls analyses (average follow-up = 11.9 $\pm$ 0.8 months). Fractures were confirmed by review of radiographic reports. All first hip fractures occurring after the fourth examination and before April 25, 2005 were included in analyses examining the association between frailty and risk of first hip fracture. Any nonspine fractures during this period were included in the analyses examining the relationship between frailty and risk of any nonspine fracture. Average follow-up was 8.9 $\pm$ 3.2 years for hip fracture and 7.6 $\pm$ 3.8 years for any nonspine fracture. Deaths were identified by contacts every 4 months and confirmed with death certificates. Follow-up for vital status was 99% complete. Average follow-up for death was 9.2 $\pm$ 3.0 years.

Statistical Analysis

Chi-square tests of homogeneity, analyses of variance, and Kruskal–Wallis tests were used to compare characteristics of participants at the fourth examination by category of frailty indicator.

Age-adjusted fracture and mortality rates were calculated. We used logistic regression to analyze the association between frailty indicators and the odds of recurrent falls ($\geq$ 2 vs $\leq$ 1) in the subsequent year. Cox proportional hazards models were used to analyze the associations between frailty indicators and subsequent outcomes including first hip fracture, any incident nonspine fracture, and death. The relative risk (approximated as hazard ratios [HR] or

odds ratios [OR]) of each outcome with 95% confidence intervals (CI) was estimated for women categorized as intermediate and those categorized as frail using women who were categorized as robust as the referent group.

Models were initially adjusted for age. To determine whether frailty was independently associated with the outcomes of frequent falls, fractures, and death, we subsequently added covariates to models that included age as a predictor. To examine whether the association between frailty indicators and increased risk of adverse health outcomes persisted among the oldest old, secondary analyses were performed stratifying participants by age ($<$ 80 years vs $\geq$ 80 years). Similarly, based on evidence of associations between frailty and underweight and between frailty and obesity, analyses were performed to determine whether relationships between frailty indicators and outcomes were consistent across categories of BMI ($<$ 18.5 kg/m^2 [underweight], 18.5–24.9 kg/m^2 [normal weight], 25.0–29.9 kg/m^2 [overweight], and $\geq$ 30 kg/m^2 [obese]). We tested for interactions between the frailty index (ordinal variable with three levels) and age, and between the frailty index and BMI for prediction of a given outcome. To assess if any relationship between frailty indicators and risk of nonspine fracture was due to an increased risk of hip fracture, the association between frailty indicators and risk of nonhip nonspine fracture was analyzed by excluding women with prior ($n = 237$) or incident hip fracture ($n = 668$). To examine the effect of fall history on the relationship between frailty indicators and frequent falls, an analysis was performed stratifying participants by history of any fall in the previous year (yes vs no). To determine whether associations between frailty indicators and risk of hip fracture varied by fracture location, we analyzed the association between frailty indicators and risk of trochanteric fracture and that between frailty indicators and risk of femoral neck fracture.

The 6724 women eligible for the primary analyses had three or more nonmissing components among the five criteria in the frailty index. For each of the 605 women (9%) missing one component and each of the 182 women (3%) missing two components, missing values of components were imputed using the mean of the nonmissing components for that participant. To examine whether the inclusion of the 781 women with missing data biased our findings regarding the associations between frailty and outcomes, we performed a secondary analysis restricted to the 787 women missing one or two components and a secondary analysis restricted to the 5937 women with all five components. Within each of these subcohorts, frail women compared with robust women had similarly increased age-adjusted risks of adverse outcomes (recurrent falls, hip fracture, any nonspine fracture, death). Hence, results of the primary analyses are presented in this article.

Results

Characteristics of the Study Population

Characteristics of the overall cohort of 6724 women and the cohort by category of frailty are shown in Table 1. Compared with the 6724 women included in this analysis who provided data for at least three frailty components, the 1688 women missing data on three or more components were more likely to die during follow-up (52% vs 38%, $p <$ .001), but were no more likely to experience a first hip fracture (11% vs 10%, $p = .685$).

Frailty and Risk of Recurrent Falls

During an average follow-up of 11.9 months, 736 (11%) women experienced $\geq$ 2 (recurrent) falls. Compared with robust women, women in the intermediate group (OR = 1.23, 95% CI, 1.02–1.48) and frail women (OR = 2.41, 95% CI, 1.93–3.01) had an increased age-adjusted odds of recurrent falls. After further adjustment for multiple potential confounders, the associations were diminished in magnitude, but the OR for frail women (1.38, 95% CI, 1.02–1.88) remained significant (Table 2).

The associations between frailty indicators and recurrent falls appeared stronger among women $\geq$ 80 years old than among those $<$ 80 years old ($p = .027$ for interaction term). In contrast, the frailty index was associated with recurrent falls among women with and without a fall history ($p = .586$ for interaction term). Frailty appeared to increase the odds of recurrent falls across all categories of body weight, though the association did not reach significance among the 124 underweight women (age-adjusted OR = 2.54, 95% CI, 0.47–13.87 among underweight women; 3.61, 95% CI, 2.51–5.17 among normal weight women; 1.95, 95% CI, 1.32–2.88 among overweight women; and 1.68, 95% CI, 1.05–2.68 among obese women). There was some evidence that the effect of frailty on odds of recurrent falls was less pronounced among overweight and obese women ($p = .009$ for interaction term).

Frailty and Risk of Fracture

During an average follow-up of 9 years, 2106 (31%) women experienced $\geq$ 1 nonspine fracture, including 668 (10%) women who suffered a first hip fracture. Of the 668 women with first incident hip fracture, 346 had femoral neck fractures and 311 had trochanteric fractures.

Compared with robust women, women in the intermediate group (HR = 1.34, 95% CI, 1.12–1.60) and frail women (HR = 1.70, 95% CI, 1.35–2.15) had an increased age-adjusted risk of hip fracture. Adjustment for multiple factors including femoral neck bone density did not entirely explain the observed associations (multivariate HR [MHR] = 1.27, 95% CI, 1.04–1.56 for women in the intermediate group and MHR = 1.40, 95% CI, 1.03–1.90 for frail women; Table 3). The associations between frailty indicators and risk of hip fracture appeared slightly greater in magnitude for trochanteric fractures (MHR, 95% CI, 1.39 [1.03–1.88] for women in the intermediate group and 1.47 [0.94–2.30] for frail women) than for femoral neck fractures (MHR, 95% CI, 1.19 [0.91–1.57] for women in the intermediate group and 1.28 [0.84–1.97] for frail women).

Frailty indicators were similarly associated with an increased risk of hip fracture among women $<$ 80 years old and those $\geq$ 80 years old ($p = .807$ for interaction term). Although the rates of hip fracture were highest in magnitude among underweight frail women and obese frail women,

Table 1. Characteristics of Participants for Overall Cohort and by Category of Frailty

Variable	Overall Cohort ($N = 6724$)	Category of Frailty: Robust ($N = 2466$)	Intermediate ($N = 3162$)	Frail ($N = 1096$)	p Value
Age, y, mean ± *SD*	76.7 ± 4.9	75.3 ± 3.9	76.8 ± 4.7	79.9 ± 5.6	< .001
Self-reported health status, %					< .001
Excellent or good	81	95	78	56	
Fair	17	5	21	35	
Poor or very poor	2	0	1	8	
Smoking status, %					.017
Current	6	5	6	7	
Former	33	33	34	30	
Never	61	62	60	63	
Current estrogen use, %	18	19	19	15	.036
Education, y, mean ± *SD*	12.8 ± 2.8	13.0 ± 2.7	12.8 ± 2.8	12.2 ± 2.9	< .001
Any fracture since age 50, %	47	42	48	56	< .001
Selected medical conditions, %*					< .001
None	34	44	32	19	
1–2	58	53	60	63	
≥ 3	8	3	9	17	
Any fall in previous year, %	30	26	30	41	< .001
Depressive symptoms					
Geriatric Depression Scale score 0–15, mean ± *SD*	1.9 ± 2.3	0.6 ± 1.0	2.2 ± 2.2	3.9 ± 2.8	< .001
Cognitive function					
Mini-Mental Status Examination score 0–26, mean ± *SD*	24.4 ± 1.9	24.7 ± 1.6	24.5 ± 1.9	23.7 ± 2.6	< .001
IADL impairments range 0–5, mean ± *SD*	0.7 ± 1.2	0.2 ± 0.5	0.6 ± 1.1	2.1 ± 1.6	< .001
Body mass index, kg/m^2, mean ± *SD*	26.5 ± 4.8	26.1 ± 4.2	26.6 ± 4.8	26.9 ± 5.5	< .001
Femoral neck bone mineral density, g/cm^2, mean ± *SD*	0.63 ± 0.12	0.64 ± 0.11	0.63 ± 0.12	0.61 ± 0.12	< .001

Notes: *History of one or more selected medical conditions including stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and nonskin cancer.

SD = standard deviation; IADL = instrumental activities of daily living.

there was no statistical evidence of an interaction between the frailty index and BMI for the prediction of hip fracture risk ($p = .681$ for interaction term).

Frailty was also independently associated with an increased risk of any nonspine fracture (MHR = 1.25, 95% CI, 1.05–1.49; Table 4). The association between frailty indicators and an increased risk of any nonspine fracture was consistently observed among women < 80 years old, among women ≥ 80 years old ($p = .584$ for interaction term), and across categories of body weight ($p = .675$ for interaction term). When women with a prior or incident hip fracture were excluded from the analysis, the relationship between frailty and risk of fracture was smaller in magnitude and did not reach significance (MHR = 1.18, 95% CI, 0.93–1.49 for any nonhip nonspine fracture).

Frailty and Risk of Mortality

Among the 6724 women followed-up for an average of 9 years, there were 2520 deaths. Increasing evidence of frailty was strongly associated with higher all-cause

Table 2. Frailty Status and Risk of Recurrent Falls in Overall Cohort and Risk Subgroup

Category of Frailty	No. with ≥ 2 Falls (%)	OR (95% CI): Overall Cohort ($N = 6543$)*	Age Category: < 80 Years ($N = 4879$)	Age Category: ≥ 80 Years ($N = 1664$)	Fall in Past Year: Yes ($N = 1986$)	Fall in Past Year: No ($N = 4546$)
Robust ($n = 2406$)	200 (8)	1.00	1.00	1.00	1.00	1.00
Intermediate ($n = 3092$)	325 (11)	0.90 (0.72–1.12)	0.84 (0.65–1.07)	1.27 (0.79–2.05)	0.96 (0.70–1.33)	0.85 (0.62–1.15)
Frail ($n = 1045$)	211 (20)	1.38 (1.02–1.88)	1.31 (0.88–1.94)	1.96 (1.14–3.37)	1.23 (0.79–1.91)	1.39 (0.89–2.18)

Notes: Odds ratios (OR) were adjusted for age; health status; smoking; estrogen use; education; history of fracture; selected medical conditions including stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and nonskin cancer; depressive symptoms; cognitive function; functional status; body mass index; and femoral neck bone mineral density.

*Among the 6724 women with at least three frailty components, 181 who did not provide fall information at follow-up contacts during the subsequent year were excluded from this analysis.

CI = confidence interval.

Table 3. Frailty Status and Risk of Hip Fracture in Overall Cohort and Risk Subgroup

				HR (95% CI)					
	Overall Cohort ($N = 6467$)*			Age Category		Category of Body Mass Index			
Category of Frailty	No. with First Hip Fracture (%)	Age-Adjusted Rate per 1000 Person-Years	HR (95% CI)	< 80 Years ($N = 4855$)	≥ 80 Years ($N = 1612$)	< 18.5 kg/m^2 ($N = 118$)	18.5–24.9 kg/m^2 ($N = 2536$)	25.0–29.9 kg/m^2 ($N = 2369$)	≥ 30 kg/m^2 ($N = 1340$)
Robust ($n = 2422$)	195 (8)	9.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate ($n = 3047$)	336 (11)	12.2	1.27 (1.04–1.56)	1.24 (0.97–1.58)	1.59 (1.09–2.31)	1.40 (0.24–8.18)	1.16 (0.88–1.53)	1.21 (0.86–1.71)	2.61 (1.28–5.31)
Frail ($n = 998$)	137 (14)	15.7	1.40 (1.03–1.90)	1.65 (1.09–2.49)	1.72 (1.08–2.75)	8.45 (1.13–62.98)	1.09 (0.72–1.65)	1.43 (0.84–2.45)	3.16 (1.17–8.58)

Notes: Hazard ratios (HR) were adjusted for age; health status; smoking; estrogen use; education; history of fracture; selected medical conditions including stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and nonskin cancer; fall history; depressive symptoms; cognitive function; functional status; body mass index; and femoral neck bone mineral density.

*Among the 6724 women with at least three frailty components, 257 were excluded from this analysis (237 women with prior hip fracture, 5 women with incident traumatic hip fracture and 15 women with unconfirmed hip fracture).

CI = confidence interval.

Table 4. Frailty Status and Risk of Any Nonspine Fracture in Overall Cohort and Risk Subgroup

				HR (95% CI)	
	Overall Cohort ($N = 6227$)*			Age Category	
Category of Frailty	No. with ≥ 1 Nonspine Fracture (%)	Age-Adjusted Rate per 1000 Person-Years	HR (95% CI)	< 80 Years ($N = 4638$)	≥ 80 Years ($N = 1589$)
Robust ($n = 2298$)	706 (31)	39.5	1.00	1.00	1.00
Intermediate ($n = 2920$)	1015 (35)	45.7	1.11 (0.99–1.24)	1.08 (0.95–1.22)	1.23 (0.98–1.55)
Frail ($n = 1009$)	385 (38)	60.7	1.25 (1.05–1.49)	1.30 (1.03–1.63)	1.33 (1.00–1.78)

Notes: Hazard ratios (HR) were adjusted for age; health status; smoking; estrogen use; education; history of fracture; selected medical conditions including stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and nonskin cancer; fall history; depressive symptoms; cognitive function; functional status; body mass index; and femoral neck bone mineral density.

*Among the 6724 women with at least three frailty components, 497 were excluded from this analysis (123 with an unconfirmed vertebral fracture, 53 with a confirmed vertebral fracture, 59 with a traumatic nonspine fracture, and 262 with an unconfirmed nonspine fracture).

CI = confidence interval.

Table 5. Frailty Status and Risk of Death in Overall Cohort and Risk Subgroup

	Overall Cohort ($n = 6724$)			HR (95% CI)					
				Age Category		Category of Body Mass Index			
Category of Frailty	No. of Deaths (%)	Age-Adjusted Rate per 1000 Person-Years	Hazard Ratio (95% CI)	< 80 Years ($N = 4997$)	≥ 80 Years ($N = 1727$)	< 18.5 kg/m^2 ($N = 131$)	18.5–24.9 kg/m^2 ($N = 2660$)	25.0–29.9 kg/m^2 ($N = 2449$)	≥ 30 kg/m^2 ($N = 1375$)
Robust ($n = 2466$)	594 (24)	28.3	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate ($n = 3162$)	1209 (38)	41.2	1.32 (1.18–1.48)	1.27 (1.11–1.46)	1.60 (1.31–1.97)	1.63 (0.67–3.95)	1.50 (1.26–1.78)	1.18 (0.98–1.41)	1.13 (0.86–1.48)
Frail ($n = 1096$)	717 (65)	76.3	1.82 (1.56–2.13)	2.03 (1.65–2.50)	2.14 (1.68–2.73)	2.51 (0.86–7.35)	2.04 (1.60–2.60)	1.48 (1.14–1.93)	1.80 (1.28–2.53)

Notes: Hazard ratios (HR) were adjusted for age; health status; smoking; estrogen use; education; history of fracture; selected medical conditions including stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and nonskin cancer; fall history; depressive symptoms; cognitive function; functional status; body mass index; and femoral neck bone mineral density.
CI = confidence interval.

mortality rates (Table 5). Compared with robust women, women in the intermediate group had a 1.3-fold increase in risk (MHR = 1.32, 95% CI, 1.18–1.48), and women classified as frail had a 1.8-fold increase in risk (MHR = 1.82, 95% CI, 1.56–2.13).

The associations between frailty indicators and mortality appeared slightly greater in magnitude among women ≥ 80 years old than among women < 80 years old (Table 5). However, there was not strong evidence of an interaction between the frailty index and age for the prediction of mortality ($p = .137$ for interaction term). The association between frailty indicators and an increased risk of death appeared generally consistent across subgroups defined by BMI ($p = .350$ for interaction term).

Discussion

Increasing evidence of frailty was independently associated with increased risks of subsequent falls, fractures, and all-cause mortality in this cohort of older women, including among very elderly women and obese older women.

These results confirm the predictive validity of the phenotype of frailty as defined by Fried and colleagues (3) in their analysis of a cohort of 5317 adults ≥ 65 years old enrolled in the CHS. After adjustment for multiple potential confounders, this phenotype was similarly associated with increased risks of falls and mortality in both cohorts. In addition, the magnitude of the association between frailty and hip fracture in this cohort was similar to that reported by the Women's Health Initiative (WHI) Observational Study (4). Women in the intermediate group in this cohort appeared to have risks of adverse health outcomes that were between those of robust women and those of frail women. These findings are in agreement with prior studies (3,4,15) using the CHS frailty phenotype.

While results of this study are in general agreement with those of previous studies examining the association between frailty and adverse health outcomes in older people, this investigation extends the work of previous studies in several ways. Although a number of studies have indicated that frailty defined in variable ways is increasingly common with advancing age (3–5), these results suggest that the independent associations between frailty and risks of recurrent falls, death, and fracture persist among very elderly women. The magnitude of the associations between frailty and risks of death and fracture, including hip fracture, appeared to be similar among women ≥ 80 years old and those 69–79 years old. In addition, the association between frailty and recurrent falls was even more pronounced for women aged 80 years and older compared with younger older women.

While being underweight, experiencing weight loss, and/or having sarcopenia have been considered to be common manifestations of frailty in older adults(16–19), a large cross-sectional study of older women with BMI ≥ 18.5 kg/m^2 (8) noted a high prevalence of frailty among obese older women. In the present prospective study of older women followed prospectively for outcomes, frailty was similarly associated with an increased risk of subsequent mortality

across categories of body weight. The association between frailty and risk of hip fracture was most pronounced among underweight women and among obese women with smaller increases in risk among normal weight and overweight women. Although there was no statistical evidence of an interaction between the frailty index and BMI for the prediction of hip fracture risk, the power to detect this interaction was limited. Frail women had an increased risk of recurrent falls across categories of body weight, though the magnitude of the association was less pronounced among heavier women.

Although frailty was independently related to hip fracture risk in this cohort of older women despite adjustment for strong risk factors including low bone density, the results suggest that it is only weakly related to other types of fracture. As reported in prior epidemiologic reviews (20,21), there may be heterogeneity in the relationship between a risk factor and skeletal fragility. In addition, the magnitude of the association between frailty and increased risk of hip fracture appeared slightly greater for trochanteric hip fractures than for femoral neck fractures. Previous studies comparing differences in risk factor patterns between femoral neck and trochanteric fractures (22–24) have consistently reported that women with trochanteric fractures are more likely to be older and have poorer health status and lower bone density.

Frailty in older people may be associated with increased risks of adverse health outcomes in older women including falls, fracture, and mortality for several reasons. Frailty has been linked to declines in circulating levels of gonadal hormones, 25-hydroxyvitamin D, growth hormone, and insulin-like growth factor-1 (IGF-1) (25–27); elevations in pro-inflammatory cytokines and coagulation factors (26,28–30); subclinical anemia (31); renal insufficiency (32); atherosclerosis (33); and anorexia and malnutrition (34). Alternatively, frailty may be a marker of other conditions that increase the risk of falls, fractures, and mortality. However, adjustment for several risk factors including advanced age, poorer health status, higher prevalence of medical comorbidities, greater depressive symptoms, poorer cognitive function, disability, BMI, and lower hip bone mineral density in this study did not entirely explain the observed higher rates of adverse health outcomes in frail older women. These findings lend support to the hypothesis that frailty in older adults is a unique disorder that is not entirely explained by advanced age, specific disease states, and/or degree of disability.

This study has a number of strengths including its prospective design, comprehensive set of measurements performed blinded to outcome status, and length and completeness of follow-up. However, this study has several limitations. Participants were elderly Caucasian women living in the community, and our results may not be applicable to other population groups. Adjusting our analyses for factors such as IADL limitations and depressive symptoms may have biased our estimates of the associations toward the null hypothesis. These results may also underestimate the association between frailty and risk of mortality because women missing three or more frailty components not included in the analyses were at highest risk for death. Inclusion of women missing one or two frailty components in the analyses may have resulted in misclassification of women with respect to the intermediate group and frailty categories. While some misclassification may have occurred, this is unlikely to have been frequent because missing values of components were imputed using the mean value of nonmissing components for each participant and classification of a participant into either the intermediate (1–2 components) or frail category (3, 4, or 5 components) involved the collapsing of components. In addition, findings from sensitivity analyses indicated that inclusion of women with missing data is unlikely to have biased our findings regarding the association between frailty and increased risk of outcomes. Power for evaluating associations between frailty and outcomes was limited in some risk subgroups, such as underweight women. Although we queried participants every 4 months by postcard or phone, falls may have been underreported (35). Finally, we defined frailty using a standard definition, but frailty is frequently defined variably and our findings may not generalize across different definitions.

Frail older women are at increased risk of recurrent falls, fractures, and mortality. This association is consistent across categories of age and body weight. Future research should compare the predictive ability of different frailty indices and identify the biologic and physiologic changes underlying the disorder.

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Correspondence

Address correspondence to Kristine E. Ensrud, MD, MPH, One Veterans Drive, Minneapolis, MN 55417. E-mail: ensru001@umn.edu

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